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(72) Inventors: KARRAR AHMAD KHAN
STUART ANTHONY HILL

(19)

(54) PHARMACEUTICAL COMPOSITIONS

(71) We, BEECHAM GROUP LIMITED, of Beecham House, Great West Road, Brentford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

The present invention relates to orally administrable antibiotic compositions.

It has been known for some time that the release rate of medicaments from certain pharmaceutical capsules can be enhanced by including disintegrants. We have now discovered that a particular release improving agent can be used with a particular group of medicaments to provide a composition with improved disintegration properties.

The present invention provides a pharmaceutical composition which comprises a hard gelatin capsule which contains an intimate mixture of an orally administrable penicillin or cephalosporin and from 1 - 8% of cross-linked insoluble polyvinylpyrrolidone.

All percentages herein are weight/weight based on the weight of penicillin or cephalosporin present.

The term 'orally administrable penicillin or cephalosporin' means any such compound known to be suitable for administration per os.

The term 'cross-linked insoluble polyvinylpyrrolidone' when used herein means a pharmaceutically acceptable polymer of vinylpyrrolidone which is insoluble in water, juices of the gastro-intestinal tract and conventional organic solvents used in the pharmaceutical industry and which may be produced by the methods disclosed in U.S. Patent Specification No. 2938017. A suitable material may be obtained from GAF (Great Britain) Ltd., Manchester, U.K., as 'Plasdone XL' (Registered Trade Mark).

Cross-linked insoluble polyvinylpyrrolidone has not previously been recommended for use in pharmaceutical capsules and has not previously been recommended as a release improving agent for use in conjunction with penicillins or cephalosporins.

The intimate mixture of penicillin or cephalosporin and cross-linked insoluble polyvinylpyrrolidone will be a powder blend which has been densified. Densification is normally achieved by either (a) compaction of a mixture of the penicillin or cephalosporin and cross-linked insoluble polyvinylpyrrolidone in a press followed by milling to form fine particles or (b) compaction of the penicillin or cephalosporin, followed by milling and blending with compacted and milled cross-linked polyvinylpyrrolidone. Process (a) yields material which we term 'intragranular' while process (b) yields material which we term 'extragranular'. Favoured compositions of this invention will contain penicillin or cephalosporin together with intragranular cross-linked insoluble polyvinylpyrrolidone.

If desired up to 10% of conventional pharmaceutical excipients may be included in the composition of the invention but in general 0 - 3% of such excipients is preferred.

Suitable penicillins and cephalosporins for use in this invention include cloxacillin, dicloxacillin, flucloxacillin, ampicillin, amoxycillin, carbenicillin α-phenyl and α-indanyl esters, ticarcillin α-tolyl ester, ampicillin pivaloyloxymethyl ester, ampicillin phthalidyl ester, cephalexin and cephradin any of which may be present as a conventional salt or hydrate if desired or mixtures of such compounds.

Particularly suitable antibacterial agents for use in the composition of this invention are ampicillin, amoxycillin, cloxacillin, flucloxacillin and salts, hydrates thereof and mixtures thereof.

Most suitably the composition of this invention will comprise 2 - 4% of cross-linked

insoluble polyvinylpyrrolidone.

Preferred compositions of this invention will comprise a hard gelatin capsule containing ampicillin trihydrate or amoxycillin trihydrate and 2 - 4% of the cross-linked insoluble polyvinylpyrrolidone.

The capsules of this invention will normally contain 100 - 750 mgs. of antibiotic, more usually 200 - 600 mgs., for example, approximately 250 or 500 mgs.

In a further aspect the present invention provides a method of improving the rate of release of a penicillin or cephalosporin from an orally administrable pharmaceutical composition in the form of a hard gelatin capsule which comprises incorporating into the contents of said capsule together with and in intimate contact with the penicillin or cephalosporin an amount of 1-8% of cross-linked insoluble polyvinylpyrrolidone.

The compositions of this invention may be prepared by filling the intimate mixture of the penicillin or cephalosporin and cross-linked insoluble polyvinylpyrrolidone into hard gelatin capsules.

Any conventional blending equipment, such as ribbon mixers, paddle mixers, tumbling cones, twin shell blenders, and vertical mixers, can be used to perform the blending operation. Similarly any conventional procedure, such as roller compacting, extrusion, slugging or moist granulation, may be used for the densifying operation. Also any conventional method of filling the mixture into the capsules may be employed.

The following Examples are illustrative of the invention:

EXAMPLE 1

Gelatin capsules containing amoxycillin trihydrate and 3% cross-linked polyvinylpyrrolidone (extragranular)

Amoxycillin trihydrate was sieved and ½% of magnesium stearate as a lubricant was added. The mixture was slugged on a tablet machine and the resultant slug broken up on an Apex mill (knives forward, medium speed, sieve size 0.063 inches) and a further ½% of magnesium stearate was added. 3% w/w cross-linked polyvinylpyrrolidone was added and the mixture blended and filled into capsules using a Zanasi machine.

(Apex is a Registered Trade Mark).

EXAMPLE 2

Gelatin capsules containing amoxycillin trihydrate and 3% cross-linked polyvinylpyrrolidone (intragranular)

Amoxycillin trihydrate was sieved and ½% of magnesium stearate and 3% w/w cross-linked polyvinylpyrrolidone were added. The mixture was slugged on a tablet machine and the resultant slug broken up on an Apex mill (knives forward, medium speed, sieve size 0.063 inches) and filled into capsules using a Zanasi machine.

EXAMPLE 3

Gelatin capsules containing ampicillin trihydrate and 3% cross-linked polyvinylpyrrolidone (extragranular)

Using the method of Example 1 the above capsules containing ampicillin trihydrate were prepared.

EXAMPLE 4

Gelatin capsules containing ampicillin trihydrate and 3% cross-linked polyvinylpyrrolidone (intragranular)

Using the method of Example 2 the above capsules containing ampicillin trihydrate were prepared.

EXAMPLE 5

Demonstration of effectiveness

a. The disintegration of hard gelatin capsules containing amoxycillin trihydrate or ampicillin trihydrate were determined using the standard British Pharmacopoeia method. The results are given in Table 1.

TABLE 1

Disintegration times of hard gelatin capsules containing amoxycillin trihydrate or ampicillin trihydrate

Drug	mg. per capsule	% Cross-linked polyvinylpyrrolidone	Disintegration Time (mins.)
Amoxycillin Trihydrate	300 mg.	0%	>45
Amoxycillin Trihydrate	300 mg.	3%, Extragranular	3.0
Amoxycillin Trihydrate	300 mg.	3%, Intragranular	2.0
Ampicillin Trihydrate	250 mg.	0%	>45
Ampicillin Trihydrate	250 mg.	3%, Extragranular	3.5

b. The capsules were suspended in a dissolution medium (buffer pH.1.5) at 37°C and the time in minutes determined for 50% and 90% of the drug content to enter solution ($t_{50\%}$ and $t_{90\%}$). The results are given in Table 2.

TABLE 2

In-vitro dissolution times of ampicillin trihydrate or amoxycillin trihydrate capsules

Drug	mg. per capsule	% Cross-linked polyvinylpyrrolidone	Dissolution Time (mins) $t_{50\%}$	$t_{90\%}$
Amoxycillin Trihydrate	300 mg.	0%	27.4	>60
Amoxycillin Trihydrate	300 mg.	3%, Extragranular	4.8	32.4
Amoxycillin Trihydrate	300 mg.	3%, Intragranular	3.3	14.1
Ampicillin Trihydrate	250 mg.	0%	41.4	>60
Ampicillin Trihydrate	250 mg.	3%, Extragranular	5.5	21.0

WHAT WE CLAIM IS:-

1. A pharmaceutcial composition which comprises a hard gelatin capsule which contains an intimate mixture of an orally administrable pencillin or cephalosporin and 1 - 8% of cross-linked insoluble polyvinylpyrrolidone.

2. A composition as claimed in claim 1 which comprises cloxacillin, dicloxacillin, flucloxacillin, ampicillin, amoxycillin, carbenicillin α-phenyl ester, carbenicillin α-indanyl ester, ticarcillin α-tolyl ester, cephalexin, cephradin or a salt or hydrate of such compounds.

3. A composition as claimed in claim 1 which comprises ampicillin, amoxycillin, flucloxacillin, cloxacillin or salts or hydrates of such compounds or mixtures of such compounds.

4. A composition as claimed in any of claims 1 - 3 which comprises 2 - 4% of cross-linked insoluble polyvinylpyrrolidone.

5. A pharmaceutical composition which comprises a hard gelatin capsule containing ampicillin trihydrate or amoxycillin trihydrate and 2-4% of cross-linked insoluble polyvinylpyrrolidone.

6. A method of improving the rate of release of a penicillin or cephalosporin from an orally administrable pharmaceutical composition in the form of a hard gelatin capsule which comprises incorporating into the contents of said capsule together with and intimate contact with the penicillin or cephalosporin an amount of 1 - 8% of cross-linked insoluble polyvinylpyrrolidone.

7. A process for the preparation of a pharmaceutical composition as claimed in claim 1 which comprises filling an intimate mixture of an orally administrable penicillin or cephalosporin and 1 - 8% of cross-linked insoluble polyvinylpyrrolidone into hard gelatin capsules.

8. A pharmaceutical composition as claimed in claim 1 and substantially as described in any of Examples 1 - 4 herein.

A.W. WHITE
Chartered Patent Agent
Agent for the Applicants.

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